Phillippo, D., Dias, S., Welton, N., Taske, N., Naidoo, B., & Ades, T. (2016). *Sensitivity of treatment decisions to bias adjustment in network meta-analysis*. Abstract from 16th Biennial European Conference of the Society for Medical Decision Making, London, United Kingdom.

Sensitivity of treatment decisions to bias adjustment in network meta-analysis

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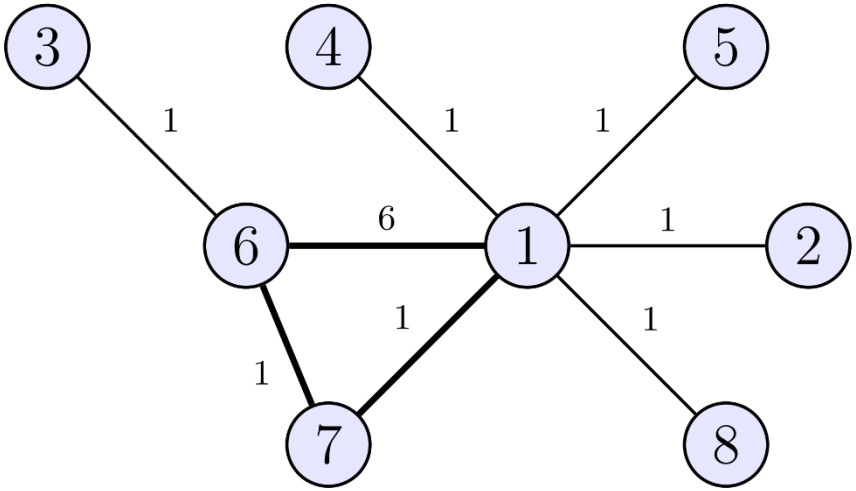
Overview

- Background and motivation
  - Network Meta-Analysis (NMA)
  - Quality vs. influence
- Threshold method
- Examples

Background – Network Meta-Analysis

- Combines evidence on multiple treatments from several studies
- Arranges treatments on a network structure joined by study evidence
- Provides consistent estimates of treatment effects
- Routinely used to inform clinical guideline recommendations, technology appraisals

Motivation – Headaches Example



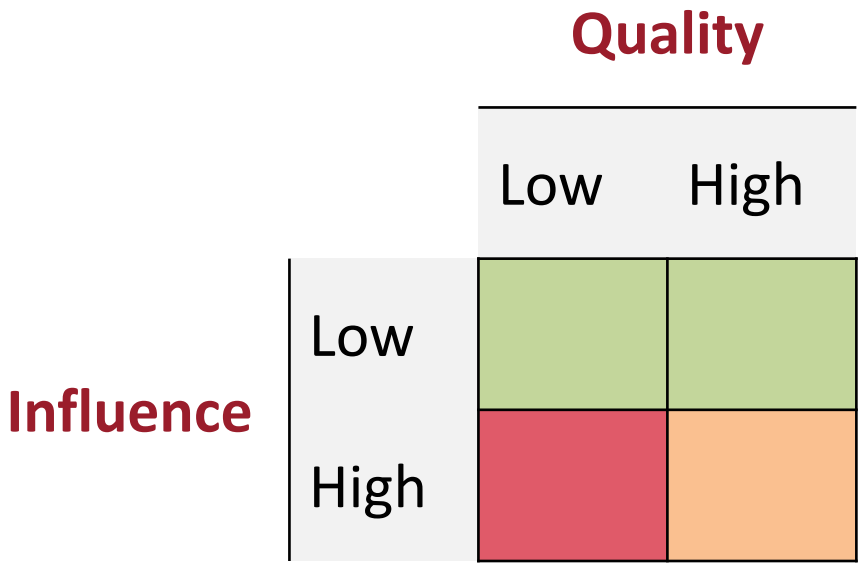
	Treatment	Mean change in headache days per month (95% CrI)
1	Placebo	0
2	Telmisartan	-0.51 (-2.32, 1.27)
3	Amitriptyline	-1.14 (-2.45, 0.16)
4	Divalproex Sodium	0.13 (-0.99, 1.23)
5	Gabapentin	0.00 (-1.60, 1.58)
6	Topiramate	-1.04 (-1.52, -0.58)
7	Propranolol	-1.19 (-2.20, -0.20)
8	Propranolol/Nadolol	-0.60 (-1.65, 0.45)

(NICE, 2015)

Motivation

How robust are the results to bias?

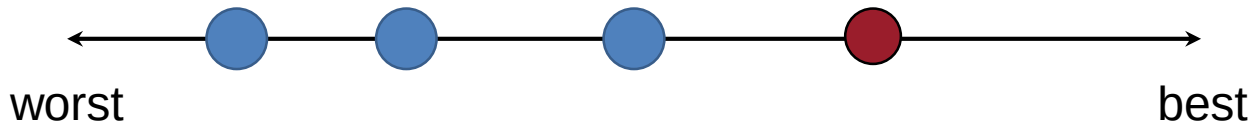
- Evidence quality is only half the story



The Threshold Method

Derive *bias adjustment thresholds*:

How much can we change a data point before the treatment recommendation changes?



The Threshold Method

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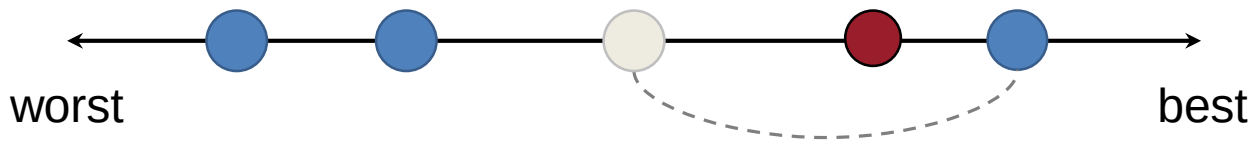
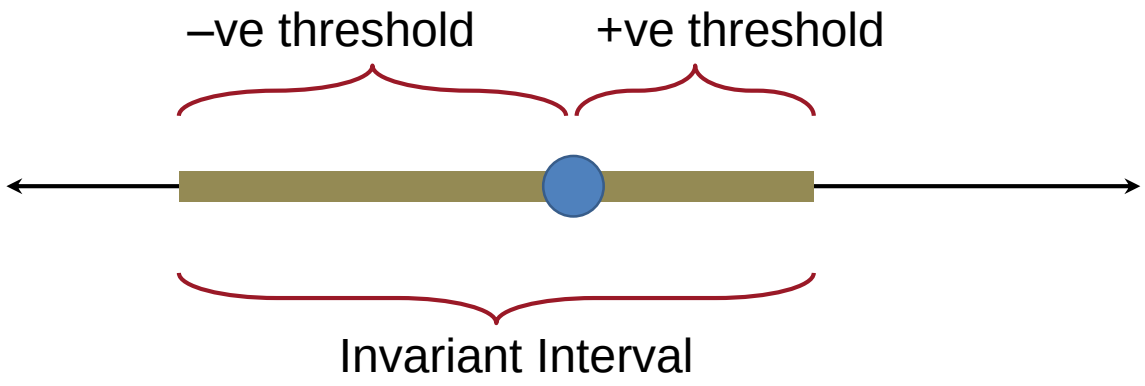


The Threshold Method

Once we have thresholds we can create a *decision invariant bias adjustment interval* for a data point

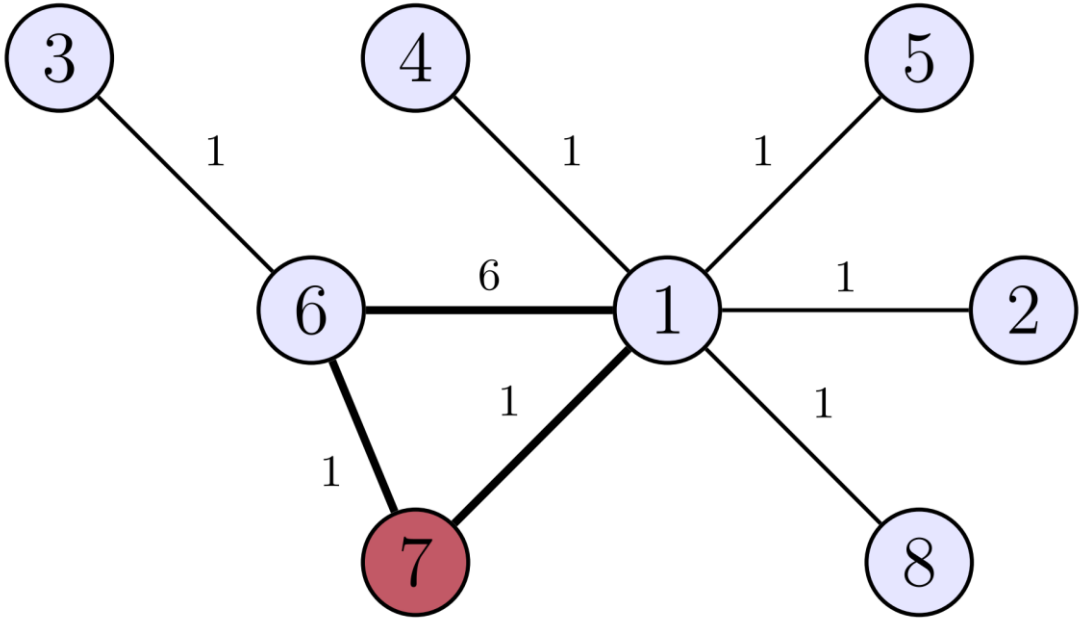


The Threshold Method

- Study level
  - Thresholds for each individual study estimate

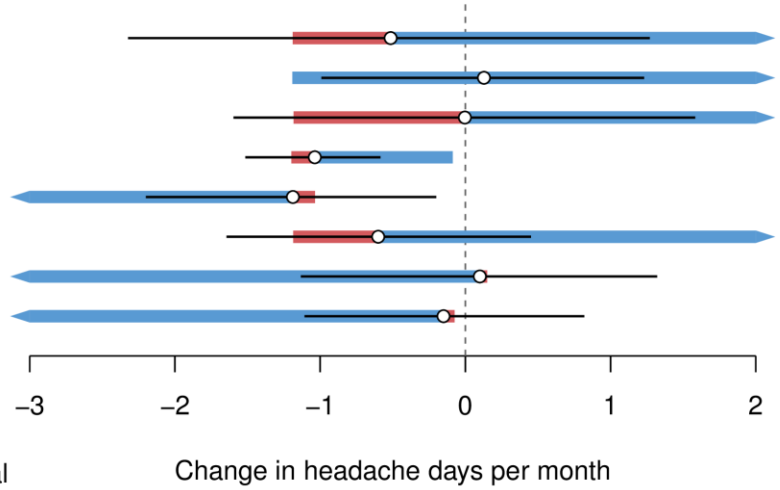
- Contrast level
  - Thresholds for combined body of evidence on a contrast
  - Highly flexible due to an approximation step

Example: Headaches



Example: Headaches – contrast level

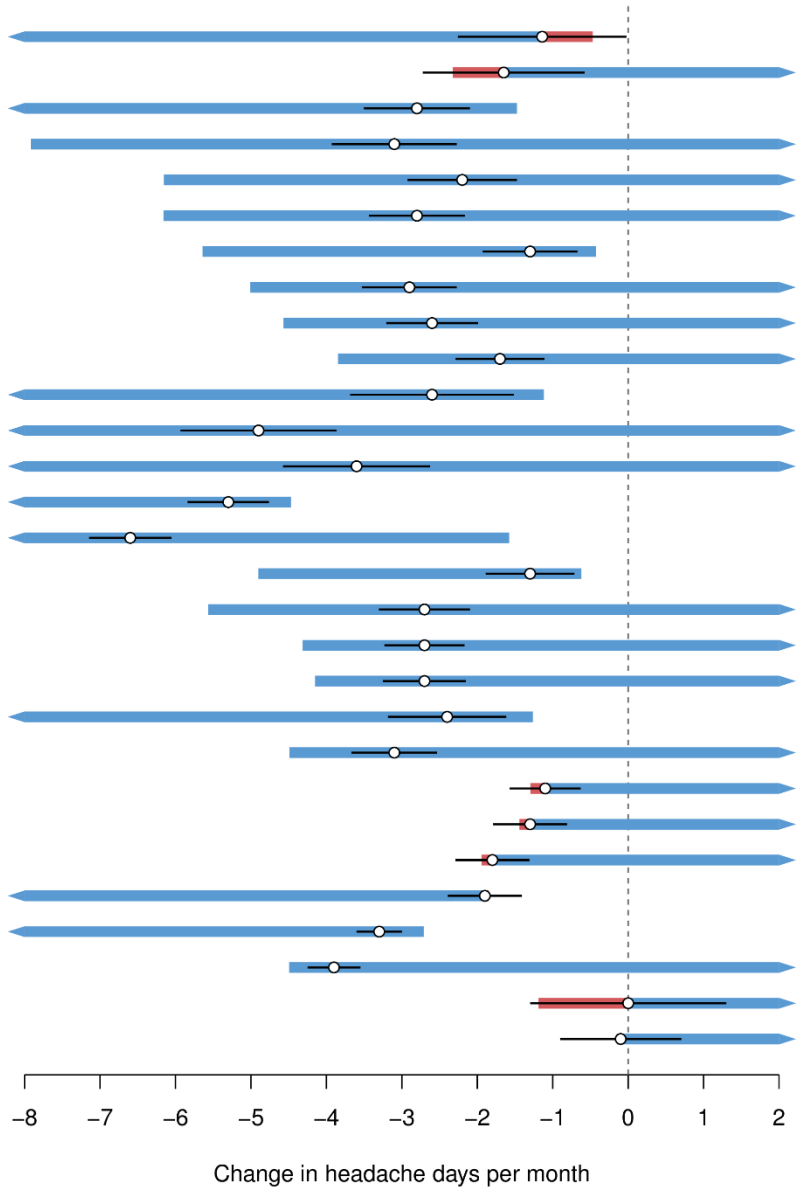
Contrast	Posterior Mean	95% Credible Interval	Invariant Interval with $\tilde{k}^*$		
2 vs. 1	–0.51	(–2.32, 1.27)	2	(–1.19, NT)	–
4 vs. 1	0.13	(–0.99, 1.23)	4	(–1.19, NT)	–
5 vs. 1	–0.00	(–1.60, 1.58)	5	(–1.18, NT)	–
†**6 vs. 1**	–1.04	(–1.51, –0.58)	3	(–1.20, –0.09)	8
†**7 vs. 1**	–1.19	(–2.20, –0.20)	–	(NT, –1.04)	3
8 vs. 1	–0.60	(–1.64, 0.45)	8	(–1.19, NT)	–
†**6 vs. 3**	0.10	(–1.13, 1.32)	–	(NT, 0.15)	3
†**7 vs. 6**	–0.15	(–1.11, 0.82)	–	(NT, –0.07)	3



Shows thresholds for changes to a body of evidence between two treatments

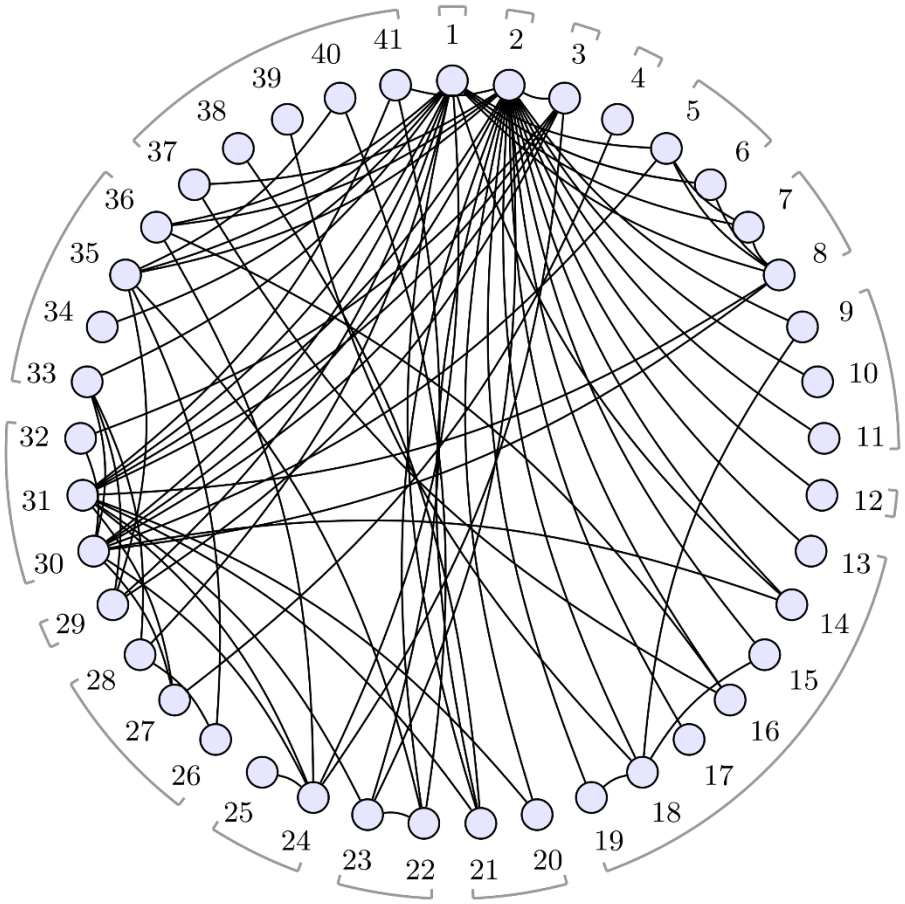
Example: Headaches – study level

Study (Trt.)	Posterior Mean	95% Confidence Interval		Invariant Interval with $\tilde{k}^*$	
Dien09 (1)	–1.14	(–2.26, –0.02)	–	(NT, –0.47)	2
Dien09 (2)	–1.65	(–2.72, –0.58)	2	(–2.32, NT)	–
Apos08 (1)	–2.80	(–3.50, –2.10)	–	(NT, –1.48)	4
Apos08 (4)	–3.10	(–3.93, –2.27)	4	(–7.92, 6.08)	3
Apos08 (4)	–2.20	(–2.93, –1.47)	4	(–6.15, 3.50)	3
Apos08 (4)	–2.80	(–3.43, –2.17)	4	(–6.16, 16.23)	3
Bran04 (1)	–1.30	(–1.93, –0.67)	8	(–5.64, –0.43)	3
Bran04 (6)	–2.90	(–3.53, –2.27)	3	(–5.01, 6.96)	8
Bran04 (6)	–2.60	(–3.21, –1.99)	3	(–4.57, 9.43)	8
Bran04 (6)	–1.70	(–2.29, –1.11)	3	(–3.85, NT)	–
Lewi09 (1)	–2.60	(–3.68, –1.52)	8	(–12.65, –1.12)	3
Lewi09 (6)	–4.90	(–5.93, –3.87)	3	(–8.24, 10.40)	8
Lewi09 (6)	–3.60	(–4.57, –2.63)	3	(–8.22, 19.98)	8
Lipt11 (1)	–5.30	(–5.84, –4.76)	8	(–11.50, –4.47)	3
Lipt11 (6)	–6.60	(–7.14, –6.06)	3	(–8.38, –1.58)	8
Silb04 (1)	–1.30	(–1.89, –0.71)	8	(–4.90, –0.62)	3
Silb04 (6)	–2.70	(–3.30, –2.10)	3	(–5.56, 9.63)	8
Silb04 (6)	–2.70	(–3.23, –2.17)	3	(–4.31, 9.00)	8
Silb04 (6)	–2.70	(–3.25, –2.15)	3	(–4.15, 8.36)	8
Winn05 (1)	–2.40	(–3.18, –1.62)	2	(–12.07, –1.26)	3
Winn05 (6)	–3.10	(–3.67, –2.53)	3	(–4.49, 5.40)	8
†**Dien04 (1)**	–1.10	(–1.57, –0.63)	3	(–1.29, NT)	–
†**Dien04 (6)**	–1.30	(–1.79, –0.81)	3	(–1.44, NT)	–
†**Dien04 (6)**	–1.80	(–2.29, –1.31)	3	(–1.94, NT)	–
†**Dien04 (7)**	–1.90	(–2.39, –1.41)	–	(NT, –1.85)	3
Holr10 (1)	–3.30	(–3.60, –3.00)	–	(NT, –2.71)	8
Holr10 (8)	–3.90	(–4.25, –3.55)	8	(–4.49, NT)	–
Silb13 (5 vs. 1)	0.00	(–1.30, 1.30)	5	(–1.19, NT)	–
†**Dodi09 (3 vs. 6)**	–0.10	(–0.90, 0.70)	3	(–0.15, NT)	–



○ Posterior Mean — 95% Confidence Interval ▬ Invariant Interval

Example: Social Anxiety

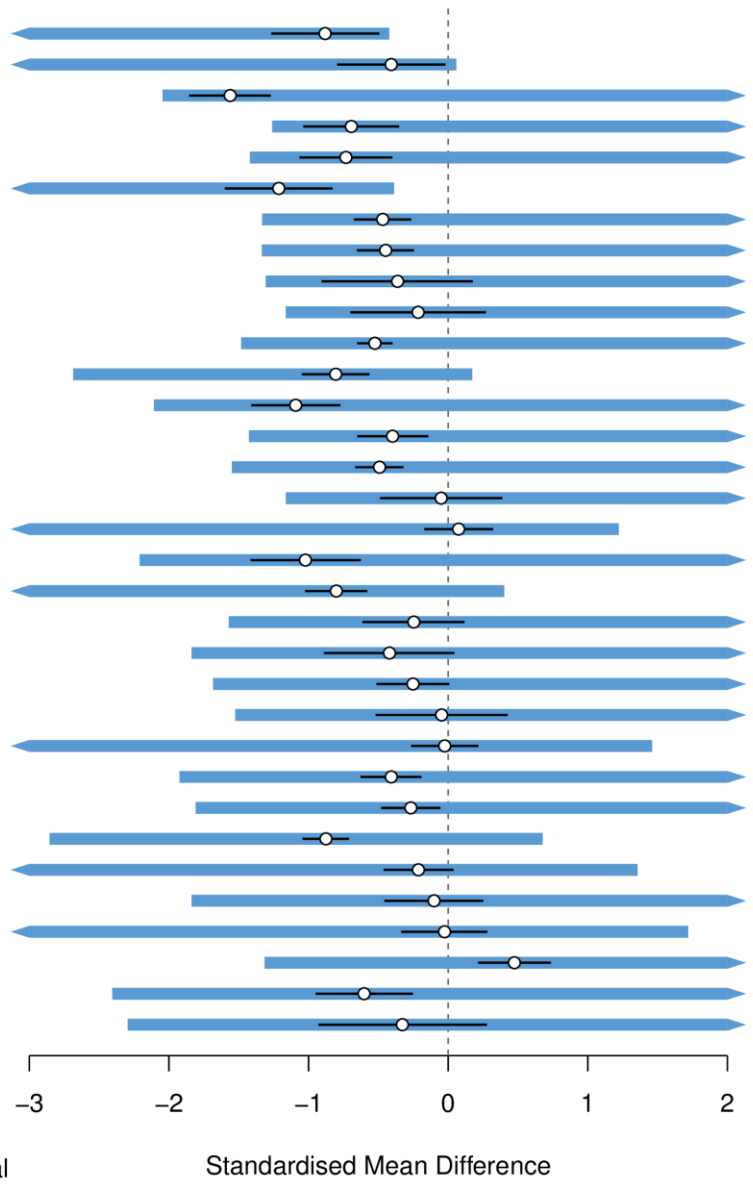


- 41 treatments, 100 studies
- Class effect model with 17 classes
- NMA fed into CEA to give decision on net benefit scale

(NCC-MH, 2013)

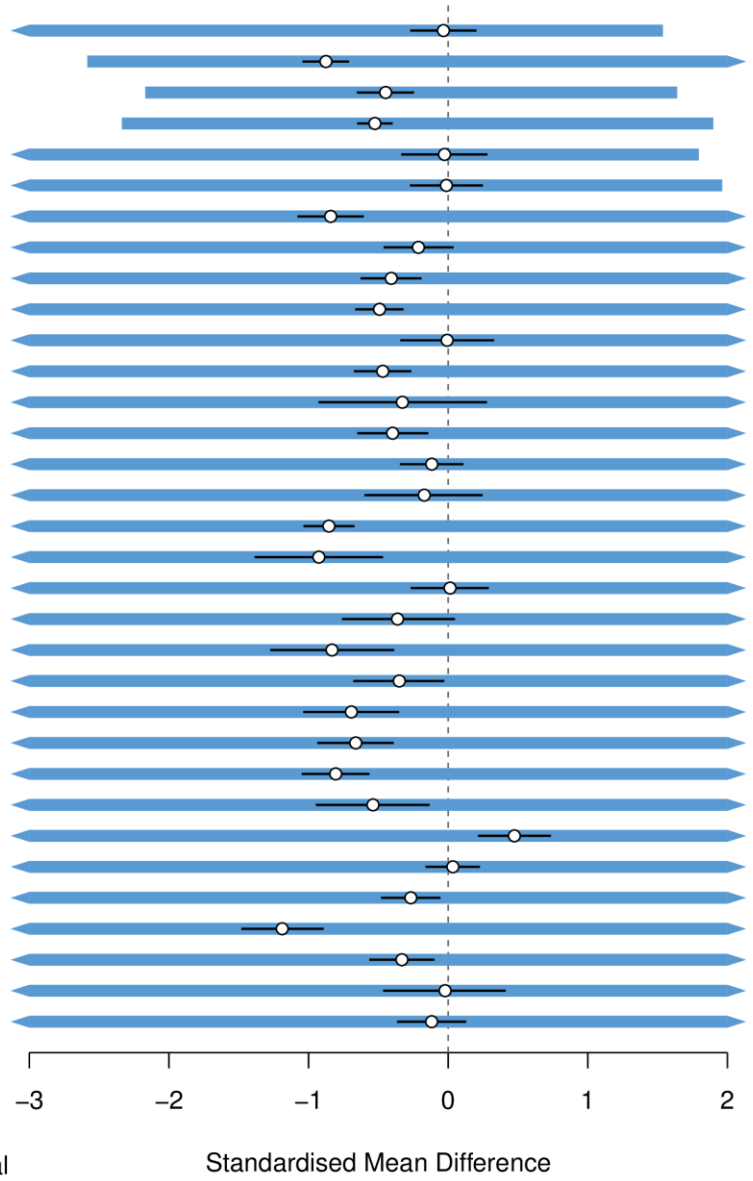
Example: Social Anxiety – contrast level (efficacy)

Contrast	Posterior Mean	95% Credible Interval	Invariant Interval with $\tilde{k}^*$		
41 vs. 31	−0.88	(−1.27, −0.49)	–	(NT, −0.42)	36
41 vs. 23	−0.41	(−0.80, −0.02)	–	(NT, 0.06)	36
36 vs. 1	−1.56	(−1.86, −1.27)	36	(−2.05, 13.61)	7
36 vs. 16	−0.69	(−1.04, −0.35)	36	(−1.26, 4.91)	16
36 vs. 24	−0.73	(−1.06, −0.40)	36	(−1.42, 5.61)	25
41 vs. 2	−1.21	(−1.60, −0.83)	–	(NT, −0.39)	36
17 vs. 2	−0.47	(−0.68, −0.26)	17	(−1.33, 50.71)	12
13 vs. 2	−0.45	(−0.65, −0.25)	13	(−1.33, 139.66)	4
39 vs. 18	−0.36	(−0.91, 0.18)	39	(−1.31, 3.60)	36
38 vs. 21	−0.22	(−0.70, 0.27)	38	(−1.16, 3.71)	36
18 vs. 2	−0.53	(−0.65, −0.40)	39	(−1.48, 8.79)	36
23 vs. 2	−0.81	(−1.05, −0.56)	23	(−2.69, 0.17)	36
36 vs. 2	−1.09	(−1.41, −0.77)	36	(−2.11, 34.05)	18
16 vs. 2	−0.40	(−0.65, −0.14)	36	(−1.43, 17.40)	12
19 vs. 2	−0.49	(−0.67, −0.32)	19	(−1.55, 29.73)	23
25 vs. 24	−0.05	(−0.49, 0.39)	25	(−1.16, 554.74)	39
31 vs. 8	0.07	(−0.17, 0.32)	31	(−13.67, 1.22)	36
34 vs. 1	−1.02	(−1.42, −0.63)	34	(−2.21, 101.29)	5
31 vs. 1	−0.80	(−1.02, −0.58)	31	(−16.38, 0.40)	36
32 vs. 30	−0.25	(−0.61, 0.12)	32	(−1.57, 5.66)	36
11 vs. 2	−0.42	(−0.89, 0.04)	11	(−1.84, 856.05)	34
9 vs. 2	−0.25	(−0.51, 0.01)	9	(−1.68, 46.63)	36
40 vs. 35	−0.05	(−0.52, 0.43)	40	(−1.53, 3.12)	36
30 vs. 24	−0.02	(−0.27, 0.22)	30	(−8.80, 1.46)	36
15 vs. 2	−0.41	(−0.63, −0.19)	15	(−1.92, 49.40)	23
22 vs. 2	−0.27	(−0.48, −0.06)	22	(−1.81, 5.92)	18
8 vs. 1	−0.88	(−1.04, −0.71)	8	(−2.86, 0.68)	36
8 vs. 6	−0.21	(−0.46, 0.04)	8	(−13.40, 1.36)	6
37 vs. 30	−0.10	(−0.46, 0.25)	37	(−1.84, 7.10)	36
8 vs. 7	−0.03	(−0.34, 0.28)	8	(−17.13, 1.72)	7
31 vs. 23	0.47	(0.21, 0.74)	36	(−1.32, 2.58)	23
21 vs. 2	−0.60	(−0.95, −0.25)	21	(−2.41, 10.57)	36
12 vs. 2	−0.33	(−0.93, 0.28)	12	(−2.30, 59.55)	36



Example: Social Anxiety – contrast level (net benefit)

Contrast	Posterior Mean	95% Credible Interval	Invariant Interval with $\tilde{k}^*$		
8 vs. 5	−0.03	(−0.27, 0.20)	5	(−6.05, 1.54)	5
8 vs. 1	−0.88	(−1.04, −0.71)	5	(−2.58, 5.66)	5
13 vs. 2	−0.45	(−0.65, −0.25)	13	(−2.17, 1.64)	13
18 vs. 2	−0.53	(−0.65, −0.40)	18	(−2.34, 1.90)	18
8 vs. 7	−0.03	(−0.34, 0.28)	–	(NT, 1.80)	7
30 vs. 5	−0.01	(−0.27, 0.25)	5	(−7.57, 1.96)	5
5 vs. 1	−0.84	(−1.08, −0.60)	5	(−3.15, 7.99)	5
8 vs. 6	−0.21	(−0.46, 0.04)	8	(−18.57, 2.19)	6
15 vs. 2	−0.41	(−0.63, −0.19)	15	(−3.31, 2.99)	15
19 vs. 2	−0.49	(−0.67, −0.32)	19	(−3.42, 2.86)	19
7 vs. 5	−0.01	(−0.34, 0.33)	7	(−3.44, 4.55)	5
17 vs. 2	−0.47	(−0.68, −0.26)	17	(−4.06, 3.34)	17
12 vs. 2	−0.33	(−0.93, 0.28)	12	(−4.27, 3.63)	12
16 vs. 2	−0.40	(−0.65, −0.14)	16	(−5.18, 5.19)	16
18 vs. 15	−0.12	(−0.35, 0.11)	15	(−5.74, 4.67)	15
28 vs. 26	−0.17	(−0.60, 0.25)	–	(NT, 4.72)	27
30 vs. 1	−0.85	(−1.04, −0.67)	5	(−6.42, 9.85)	16
35 vs. 26	−0.93	(−1.39, −0.47)	–	(NT, 4.70)	27
30 vs. 16	0.01	(−0.27, 0.29)	16	(−6.60, 5.67)	16
14 vs. 2	−0.36	(−0.76, 0.05)	14	(−7.20, 7.15)	14
14 vs. 1	−0.83	(−1.27, −0.39)	14	(−8.51, 7.60)	14
33 vs. 29	−0.35	(−0.68, −0.03)	–	(NT, 7.90)	30
36 vs. 16	−0.69	(−1.04, −0.35)	16	(−10.61, 7.78)	16
6 vs. 1	−0.66	(−0.94, −0.39)	6	(−9.17, NT)	–
23 vs. 2	−0.81	(−1.05, −0.56)	24	(−9.38, 11.46)	18
33 vs. 28	−0.54	(−0.95, −0.13)	–	(NT, 8.79)	27
31 vs. 23	0.47	(0.21, 0.74)	12	(−18.59, 9.80)	24
19 vs. 18	0.03	(−0.16, 0.23)	19	(−9.48, 10.94)	19
22 vs. 2	−0.27	(−0.48, −0.06)	12	(−13.06, 9.81)	18
35 vs. 1	−1.19	(−1.48, −0.89)	27	(−11.79, 17.33)	18
31 vs. 2	−0.33	(−0.57, −0.10)	18	(−14.95, 10.60)	18
30 vs. 14	−0.02	(−0.47, 0.41)	14	(−12.55, 11.38)	14
33 vs. 30	−0.12	(−0.37, 0.13)	–	(NT, 11.47)	5



Conclusions

- Provides insight into the effects of bias adjustment on treatment decisions
- Application to combined data on contrasts is highly flexible
- More confidence in recommendations where thresholds are large
- Focusses attention on the quality of decision-sensitive trials and contrasts

Acknowledgements

NICE
National Institute for Health and Care Excellence

This work was supported by the Centre for Clinical Practice, NICE, with funding to the Clinical Guidelines Technical Support Unit, University of Bristol.

MRC Medical Research Council

This work was undertaken with the support of the MRC ConDuCT-II Hub (MR/K025643/1), and the MRC grant MR/M005232/1.

Phillippo D M, Welton N J, Dias S, Didelez V, Ades A E. *Bias-Adjustment Thresholds for Bayesian Network Meta-Analysis*. Submitted.

Additional slides

The Threshold Method

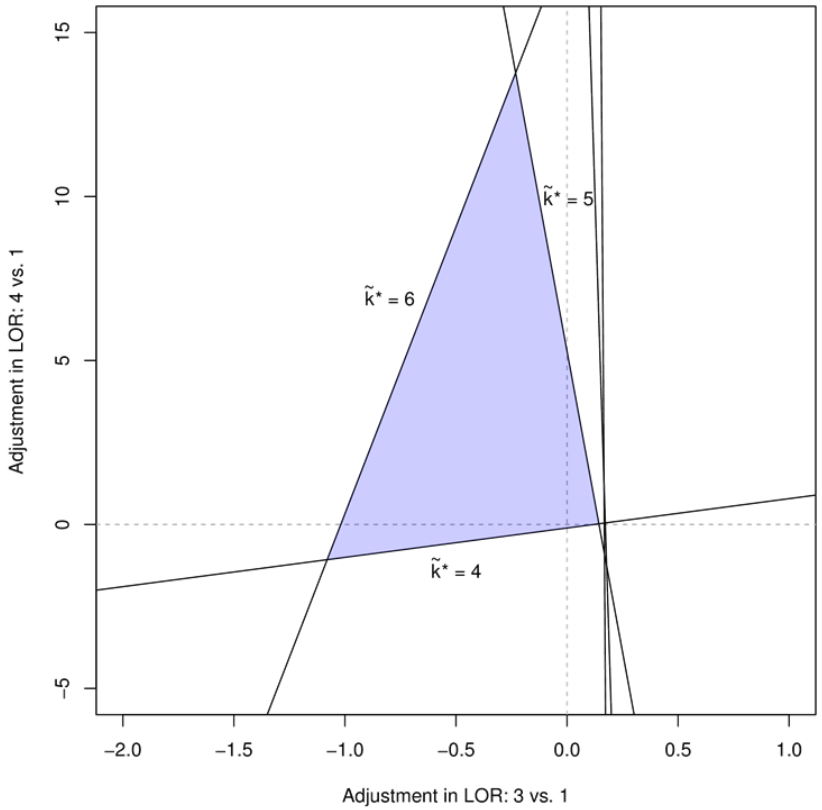
Thresholds are derived for a data point by:

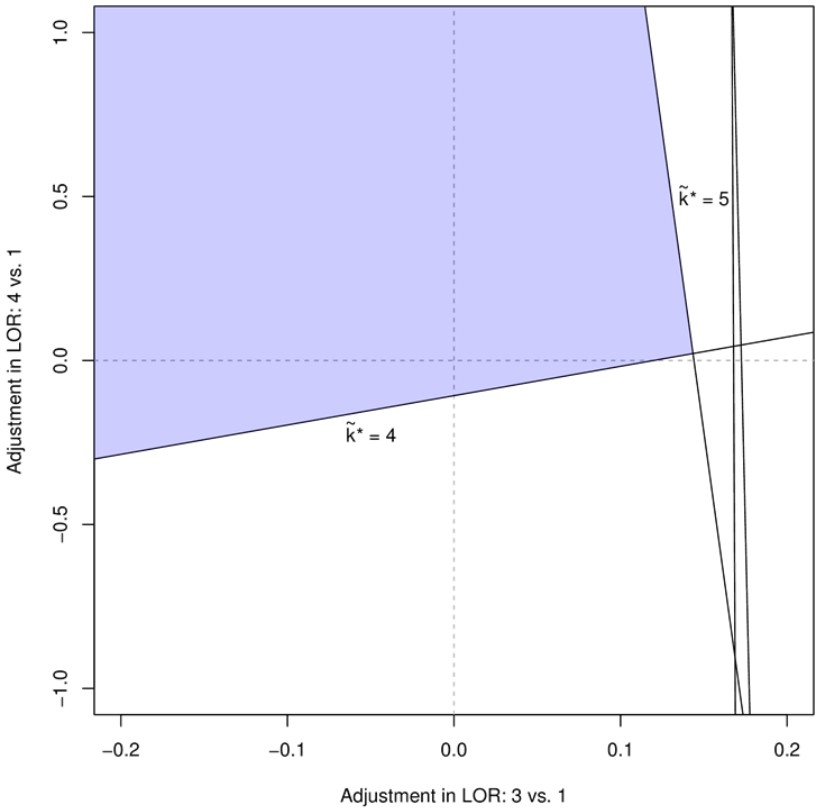
1. Asking for each non-optimal treatment how much adjustment would make that treatment optimal

$$\frac{\text{Difference to overturn}}{\text{Influence of data point}}$$

2. Taking the smallest positive and negative adjustments as the positive and negative thresholds

Extensions: Multiple simultaneous adjustments





Extensions: Psychological treatment bias